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By: Maisie C Livengood
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PATENT
Attorney Docket No.: 20695D-000110US
Client Ref. No.: US 196

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Mitterer, et al.

Application No.: TO BE ASSIGNED

Filed: HEREWITH

For: A METHOD FOR PURIFYING FACTOR VWF-COMPLEX BY MEANS OF CATION EXCHANGE CHROMATOGRAPHY

Art Unit:

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Please amend the application as follows without prejudice:

IN THE SPECIFICATION:

On page 1, after the TITLE section, please insert the following:

-- CROSS REFERENCE TO RELATED APPLICATIONS

This is a divisional of U.S. Patent Application Serial No. 09/367,459, filed May 8, 2000, which is a national phase of PCT Patent Application No. PCT/AT98/00043, filed February 27 1998, which claims priority to AT Patent Application No. A338/97 filed February 27, 1997, all of which are incorporated herein by reference in their entirety.--

IN THE CLAIMS:

Please cancel claims 1-16.

Please add new claims 17-22 as follows:

17. (New) A factor VIII/vWF-complex particularly containing high-molecular vWF multimers, obtainable from a factor VIII/vWF-containing solution by cation exchange chromatography.

18. (New) The factor VIII/v/WF-complex of Claim 17, wherein said factor VIII/vWF-complex is particularly free from low-molecular vWF multimers, inactive vWF degradation products, factor VIII free from platelet agglutinating vWF activity and factor VIIIa activity.

19. (New) The factor VIII/vWF-complex of Claim 18, wherein said factor VIII/vWF-complex has a specific vWF activity of at least 66 U/mg protein and a specific factor VIII activity of at least 500 U/mg protein.

20. (New) A preparation comprising factor VIII/vWF-complex of Claim 19, wherein said preparation is virus-safe and free from infectious material.

21. (New) The preparation of Claim 20, wherein said preparation is present in storage-stable form.

22. (New) The preparation of Claim 20, wherein said preparation is formulated as a pharmaceutical preparation.

REMARKS

This is a divisional of U.S. Patent No. 09/367,459, filed May 8, 2000, which is a national phase of PCT Patent Application No. PCT/AT98/00043, filed February 27 1998, which claims priority to AT Patent Application No. A338/97 filed February 27, 1997, all of which are incorporated herein by reference in their entirety.

PATENT

Claims 1-16 are pending in this application. Claims 1-16 have been canceled. Claims 17-22 have been added. New claims 17-22 correspond to claims 26-28, 30, 32 and 34 of the Preliminary Amendment to the parent application that was filed on August 13, 1999, which were canceled in response to the Restriction Requirement having a mailing date of September 19, 2001. Upon entry of this Preliminary Amendment, Claims 17-22 will be pending in this application.

Attached hereto as Appendix A captioned "Version with Markings to show changes made" is a marked-up version of the changes made to the claims by the current amendment.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

On page 1, after the TITLE section, the "CROSS-REFERENCE TO RELATED APPLICATION" section has been added as follows:

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a divisional of U.S. Patent Application Serial No. 09/367,459, filed May 8, 2000, which is a national phase of PCT Patent Application No. PCT/AT98/00043, filed February 27 1998, which claims priority to AT Patent Application No. A338/97 filed February 27, 1997, all of which are incorporated herein by reference in their entirety.

IN THE CLAIMS:

Claims 1-16 have been canceled.

New Claims 17-22 have been added as follows:

17. (New) A factor VIII/vWF-complex particularly containing high-molecular vWF multimers, obtainable from a factor VIII/vWF-containing solution by cation exchange chromatography.

18. (New) The factor VIII/v/WF-complex of Claim 17, wherein said factor VIII/vWF-complex is particularly free from low-molecular vWF multimers, inactive vWF degradation products, factor VIII free from platelet agglutinating vWF activity and factor VIIIa activity.

19. (New) The factor VIII/vWF-complex of Claim 18, wherein said factor VIII/vWF-complex has a specific vWF activity of at least 66 U/mg protein and a specific factor VIII activity of at least 500 U/mg protein.

20. (New) A preparation comprising factor VIII/vWF-complex of Claim 19, wherein said preparation is virus-safe and free from infectious material.

21. (New) The preparation of Claim 20, wherein said preparation is present in storage-stable form.

22. (New) The preparation of Claim 20, wherein said preparation is formulated as a pharmaceutical preparation.

Claims:

1. A method of recovering factor VIII/vWF-complex, characterized in that factor VIII/vWF-complex from a protein solution is bound to a cation exchanger and is recovered by step-wise elution of factor VIII/vWF-complex, which particularly contains high-molecular vWF-multimers.

2. A method according to claim 1, characterized in that factor VIII/vWF-complex is bound to a cation exchanger at a salt concentration of ≤ 250 mM, and factor VIII/vWF-complex containing low-molecular vWF multimers, factor VIII free from platelet agglutinating vWF activity and factor VIII:C is eluted at a salt concentration of between ≥ 250 mM and ≤ 300 mM and recovered.

3. A method according to claim 1 or 2, characterized in that factor VIII/vWF-complex particularly containing high-molecular vWF multimers is recovered by step-wise fractionation at a salt concentration of ≥ 300 mM, preferably ≥ 350 mM.

4. A method according to claim 3, characterized in

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that a factor VIII/vWF-complex-containing fraction is recovered which particularly is free from low-molecular vWF multimers and vWF degradation products, non-complexed factor VIII or factor VIII weakly bound to vWF, and contaminating nucleic acids.

5. A method according to any one of claims 1 to 4, characterized in that the elution of the polypeptides from the cation exchanger is effected in a buffer system having a pH ranging between 4.5 and 8.5, preferably ≥ 7.1 and ≤ 8.5.

6. A method according to any one of claims 1 to 5, characterized in that the cation exchanger is a sulfopropyl- or carboxymethyl-group-conjugated carrier.

7. A method according to any one of claims 1 to 6, characterized in that a factor VIII/vWF-complex particularly containing high-molecular vWF multimers is recovered.

8. A method according to any one of claims 1 to 7, characterized in that factor VIII/vWF-complex is recovered from plasma, a plasma fraction,

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cryoprecipitate, the cell-free supernatant or extract of a recombinant cell culture, or from an enriched protein fraction.

9. A factor VIII/vWF-complex particularly containing high-molecular vWF multimers, obtainable from a factor VIII/vWF-containing solution by cation exchange chromatography.

10. A factor VIII/vWF-complex according to claim 9, characterized in that it is particularly free from low-molecular vWF multimers, inactive vWF-degradation products and factor VIII free from platelet-agglutinating vWF activity and from factor VIIIa activity.

11. A factor VIII/vWF-complex according to claim 10, characterized in that it has a specific vWF activity of at least 66 U/mg protein and a specific factor VIII activity of at least 500 U/mg protein.

12. Factor VIII:C, substantially free from platelet-agglutinating vWF activity, obtainable from a factor VIII/vWF-containing solution by cation exchange

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chromatography and step-wise elution at a salt concentration of between ≥ 200 mM and ≤ 300 mM.

13. A preparation containing factor VIII/vWF-complex or factor VIII:C according to any one of claims 11 or 12, characterized in that it is virus-safe and free from infectious material.

14. A preparation according to claim 13, characterized in that it is present in storage-stable form.

15. A preparation according to any one of claims 13 or 14, characterized in that it is formulated as a pharmaceutical preparation.

16. The use of a preparation according to any one of claims 13 to 15 for producing a medicament for the treatment of patients suffering from hemophilia A, phenotypical hemophilia and vWD.

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